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The Calorimetry Experts

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July 8, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration,
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket # 2004-N-0181

Dear Sirs:

There are numerous hurdles in drug development that span various aspects of the overall drug development and approval process. The purpose of this letter is to describe two critical bottlenecks in early stage drug candidate selection and formulation stability and provide information as to how these processes can be improved.

Drug Candidate Selection
Once a target has been validated for a disease state, the commonly used approaches include high throughput screening (HTS), molecular modeling and rational drug design amongst others. HTS, while providing many "hits" has not proven to be the panacea for drug development initially hoped for, as evidenced by the dearth of new drugs developed using this approach. Molecular modeling, including structural studies, has good promise but the multitude of assumptions required often leads to erroneous results, taking development scientists down unproductive paths. The discovery process can be greatly improved by augmenting current strategies with analytical tools that provide precise and reliable data that scientists can use early in the discovery process in conjunction with other techniques that will better guide them through the decision process maze of drug candidate selection.

Microcalorimetry is an easy to use, precise analytical method that provides critical information when selecting potential drug candidates. It provides vital information not available from other techniques. A significant advantage of microcalorimetry is it performs analysis of molecular interactions using native molecules in solution, thereby avoiding artifacts caused by the need to modify or chemically immobilize one or both components of a binding pair as is required by most other analytical techniques. One type of microcalorimetry, Isothermal Titration Calorimetry (ITC), provides a complete binding profile of any molecular interaction. It is based on the well accepted principles of thermodynamics and in a single experiment provides a binding constant (K_B), enthalpy (ΔH), entropy (ΔS), stoichiometry (n) and free energy (ΔG). While many techniques can determine K_B from binding assays that rely on immobilization and labeling of one or both reagents, only ITC can provide true binding affinities using native molecules in solution. These thermodynamic parameters provide a wealth of information about mechanisms of

2004N - 0181 C 2

binding. For example, enthalpic (ΔH) driven binding is primarily caused by the formation of hydrogen and electrostatic bonds which tend to lead to highly specific binding. Entropic (ΔS) driven interactions are generally due to hydrophobic binding and tend to be non-specific. By having this information available early in the development process, development scientists will have a better understanding of the balance of forces that drive the binding of effecter molecules and their targets, resulting in the development of safer, and more efficacious drugs in a timelier manner[1,2,3].

ITC utilizes heat, the "universal detector", for studying molecular interactions. In every binding process, heat is either generated or absorbed. It is therefore applicable to low molecular weight drugs, proteins or biotechnology based therapeutics as well as vaccines. ITC has been available since 1989 and is a tried and well tested technique. The recent introduction of an automated ITC and other microcalorimetry tools lends this technology to the automation required in the drug development process. Microcalorimetry does not require further development of hardware or software and is available now. It is our opinion that ITC is a valuable addition to the drug development "toolbox" which can accelerate the early stages of the drug development process.

In our opinion, the FDA can play a valuable role by selecting the tools and techniques the Agency believes will improve the drug development process and in collaboration with third parties, establish a forum to educate drug development scientists as to the value of these technologies. As techniques and methods become widely accepted, FDA guidance and/or selection as industry standards should be decided.

Protein Formulation Stability

For biologics, i.e., proteins, vaccines and other biological macromolecules, stable formulations are a necessity for commercial therapeutics. Formulation scientists currently have only two choices; lyophilization or liquid formulations. It is generally held that liquid formulations are preferable, provided that adequately stable formulations can be developed.

Liquid formulation development today is a combination of art and experience. Formulation scientists typically develop a multitude of formulations and evaluate these using accelerated stability methods. This leads to a situation where "acceptable", but not necessarily optimal, formulations are selected for development. Accelerated stability results are at best an indication of real time stability and formulations viewed as promising by accelerated methods frequently fail real time stability studies. These failures can lead to substantial delays in the approval of promising new drugs.

Using classical thermodynamics, Differential Scanning Calorimetry (DSC) can quantitatively determine which conditions and/or additives stabilize or destabilize protein structure. When a protein solution is heated, at a given temperature it will unfold. This unfolding temperature (T_m) is easily determined by DSC microcalorimetry. Using classical thermodynamics it has been shown that anything that stabilizes protein structure causes T_m to increase and conversely, anything that destabilizes protein structure will cause T_m to decrease. Used as a pre-formulation tool, by examining an array of solution conditions, excipients and preservatives, formulation scientists can quickly determine the optimal thermodynamic conditions for protein stability and this limited number of likely formulations can be further tested using existing techniques of accelerated and real time stability studies.

By providing quantitative information relating to protein stability, DSC has demonstrated its ability to assist formulation scientists in their efforts to identify optimum formulations quickly and precisely, thus minimizing delays associated with real time stability failures[4,5]. With automated DSC currently available, higher throughput at this critical stage of development is easily achievable thereby making this a viable routine technique for the formulations scientist.

Microcalorimetric DSC instruments, available since 1977, have greatly improved over the years. Today's instruments utilize user friendly data analysis software and provide the sensitivity, precision and ease of use that can make a significant impact on the number of drugs developed and the success rate of those making it through the development and approval process.

As the FDA strives to identify hurdles and solutions that have an impact on drug development being conducted today, the role for the Agency should be to establish a broad based technology forum that can educate scientists about the use of newer technologies that have the greatest potential to accelerate drug development, and thereby the approval process.

We hope you will find this information useful in your deliberations. Please do not hesitate to contact us should you have any questions or want more detailed information on the solutions that may be provided by microcalorimetry in today's drug development efforts.

Sincerely,

William Gelb, Ph.D.
President
MicroCal, LLC

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[4] Remmele, R.L., Nightlinger, N.S., Srinivasan, S. and Gombotz, W.R. 1998. Interleukin-1 Receptor (IL-1R) liquid formulation development using differential scanning calorimetry. Pharm. Res. 15(2): 200-208.

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